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Optimised robust treatment plans for prostate cancer focal brachytherapy

John M. Betts[1], Christopher Mears[1], Hayley M. Reynolds[2,3], Guido Tack[1,4], Kevin Leo[1,4], Martin A. Ebert[5,6], and Annette Haworth[2,3]

[1] Faculty of Information Technology, Monash University, Australia
{john.betts,chris.mears,guido.tack,kevin.leo}@monash.edu
[2] Department of Physical Sciences, Peter MacCallum Cancer Centre, Victoria, Australia
{Hayley.Reynolds,Annette.Haworth}@petermac.org
[3] Sir Peter Mac Department of Oncology, The University of Melbourne, Victoria, Australia
[4] National ICT Australia
[5] Radiation Oncology, Sir Charles Gairdner Hospital, Nedlands, Western Australia
[6] School of Physics, University of Western Australia, Perth, Western Australia

Abstract

Focal brachytherapy is a clinical procedure that can be used to treat low-risk prostate cancer with reduced side-effects compared to conventional brachytherapy. Current practice is to manually plan the placement of radioactive seeds inside the prostate to achieve a desired treatment dose. Problems with the current practice are that the manual planning is time-consuming and high doses to the urethra and rectum cause undesirable side-effects. To address this problem, we have designed an optimisation algorithm that constructs treatment plans which achieve the desired dose while minimizing dose to organs at risk. We also show that these seed plans are robust to post-operative movement of the seeds within the prostate.

Keywords: optimization, brachytherapy, simulation

1 Introduction

The prostate gland is a walnut-sized organ forming part of the male genitourinary system. The prostate gland is positioned at the base of the bladder, adjacent to the rectum, with the urethra running through its center. Prostate cancer is one of the most commonly occurring cancers in males [1]. The incidence of prostate cancer varies according to a variety of factors including age, ethnicity and living conditions. Males in the developed world are most at risk with an incidence of the order of 100 new cases detected per 100,000 males annually [8].

There are a range of treatment options for localized prostate cancer (that is, cancer which has not spread beyond the prostate) including surgery and radiotherapy. Brachytherapy is a specialized type of radiotherapy whereby tiny radioactive sources (seeds) are implanted, either permanently or temporarily, into the prostate to kill the cancer cells. The side effects from this

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type of treatment vary [5]. In the case of low dose-rate permanent brachytherapy (LDR), acute urinary toxicity typically peaks in the first few months following implant with most patients returning to pre-treatment function by 12-18 months [18]. One third of LDR cases however have persistent troublesome urinary toxicity at 12 months and this is associated with larger doses to the entire prostate [5, 9]. Rectal complications are rare as long as the seeds are not placed in or adjacent to the rectal mucosa [14]. However, rectal bleeding is observed in approximately one quarter of patients receiving LDR 1 to 3 years after implantation [15, 14].

The common approach for treatment of prostate cancer uniformly targets the entire gland. In contrast, focal therapy has been proposed as an alternative treatment approach that focuses treatment on only those parts of the prostate shown on biopsy or with magnetic resonance imaging (MRI), to contain disease [10, 17]. Biopsy or imaging studies may not locate all tumor deposits, however, and since prostate cancer is a multi-focal disease it is necessary to consider not only the detected lesions but any low-volume disease that may also be within in the prostate. As a consequence, focused therapy has been proposed as a form of focal therapy whereby, in addition to delivering high doses to specific regions of the prostate, the remaining gland receives smaller doses sufficient to control low-volume disease [7].

A disadvantage of focal plans is that they are difficult to design using the current manual techniques. A further complication is that post-operative movement of the seeds can have a larger negative impact on the efficacy of the treatment than in conventional brachytherapy, due to the reduced safety margins resulting from having fewer seeds.

In response to these challenges, this paper introduces an optimization algorithm, using a biological model for its objective, to determine the optimal placement of the radioactive seeds to achieve high rates of tumor control with minimal dose to the urethra and rectum. Simulation modelling is then used to determine the efficacy of the focal models in the presence of post-operative seed displacement using estimates of variability obtained directly from clinical data.

2 Background

2.1 Prostate Brachytherapy

The brachytherapy treatment studied in this paper is based on the permanent implantation of seeds containing radioactive iodine I-125. The seeds are inserted into the patient as strands within a needle whereby active seeds are separated by inert spacers. Thus, multiple seeds can be inserted using a single needle. The treatment procedure consists of the following stages: images of the patient's prostate are made axially (parallel with the template in Figure 1) using trans-rectal ultrasound at 5mm intervals to create a 3 dimensional map of the prostate; the images of the prostate at each axial slice are overlaid with a 5mm by 5mm template defining potential needle locations; a plan is created by adding seeds to each slice using the template, following seed placement rules (described in Section 3.2), until a sufficiently high dose and Tumor Control Probability (TCP) is obtained over the prostate (the TCP calculation is described in Section 2.2). Current clinical practice is to determine seed placement manually using commercially available software to calculate radiation dose; finally, using the seed plan, needles are prepared and inserted into the patient via the perineum under anaesthesia using trans-rectal ultrasound guidance as shown in Figure 1.

2.2 The Radiobiological Model for TCP Calculation

TCP is calculated using the radiobiological model developed by Haworth et al. [6, 7]. For a prostate divided into N independent subsections (voxels), the TCP is calculated at each

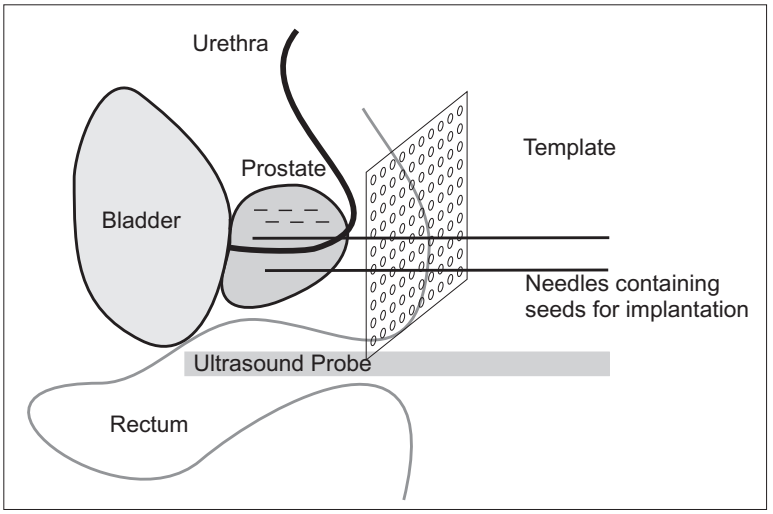

Figure 1: Prostate brachytherapy operation showing major relevant body structures, seeds implanted in prostate, seed containing needles and template.

subsection for a given level of radiosensitivity, α_k, using Equations 1 to 5.

$$TCP_i(\alpha_k) = \exp\left(-\rho_i\, V_i\, \exp\left(-\alpha_k\, d_i\, RE_i + \ln(2)\left(\frac{T^i_{crit}}{T_{pot}}\right)\right)\right), \tag{1}$$

Where

$$RE_i = 1 + \frac{2\beta R_i \lambda}{\alpha_k(\mu-\lambda)(1-\exp(-\lambda T^i_{crit}))} \times \left(\frac{1-\exp\left(-2\lambda T^i_{crit}\right)}{2\lambda} - \frac{1-\exp(-T^i_{crit}(\mu+\lambda))}{\mu+\lambda}\right) \tag{2}$$

and

$$d_i = \frac{R_i}{\lambda} - \frac{\ln(2)}{\alpha_k \lambda T_{pot}}. \tag{3}$$

Inputs to the model are: for the i^{th} subsection, ρ_i is the tumor cell density; V_i is the volume; d_i is the effective dose delivered to the subsection; R_i is the initial dose rate; T^i_{crit} is the time at which the radioactive source ceases to be effective; the constant λ is the rate at which the radioactive source decays; T_{pot} is the potential tumor regeneration rate; μ is the exponential repair rate, β is an additional radiosensitivity parameter based on tissue type. RE_i is the effectiveness of the radiation dose in retarding cell proliferation.

TCP for the whole prostate at a given level of radiosensitivity α_k is then evaluated as the product of the individual subsections, thus:

$$TCP(\alpha_k) = \prod_{i=1}^{N} TCP_i(\alpha_k). \tag{4}$$

Tumors in a single patient may contain cells with a heterogenous distribution of radiosensitivities. To account for this variability, α_k is modelled as having a discrete log-normal distribution by applying weighting factors $w(\alpha_k)$ [6]. Taking the expected value over α_k gives:

$$TCP = \sum_{k=1}^{n} w(\alpha_k)\, TCP(\alpha_k). \tag{5}$$

The radiation dose at each subsection, R_i, is the sum of radiation received from each of the implanted seeds, and is determined by the distance of the subsection from the seed according to the TG-43 formalism [13].

3 Automatic Focal Treatment Planning

The aim of focal brachytherapy is to deliver higher doses of radiation to the regions of the prostate where tumorous tissue is more likely. In typical clinical practice the seed plans are created manually, requiring the user to balance the conflicting objectives of protecting sensitive tissue, respecting planning constraints, and achieving a high chance of sterilizing any tumor.

To develop a satisfactory plan manually takes an experienced practitioner around an hour. This is too long to permit intra-operative planning, whereby plans are created at the time of the implant. Currently, a two-stage process is required, where first the planning ultrasound volume study is conducted, and some weeks later the implant is made [12]. Furthermore, the software used to create plans does not support the use of the biological model described in Section 2.2, which is a novel feature of our approach. Previous authors have applied mathematical optimization and genetic algorithms to seed placement [11]; however, the optimization is based only on dose distribution and not on a biological approach.

Our goal is to construct satisfactory robust seed plans quickly and automatically. The user specifies the patient data and planning constraints, and the system provides a seed plan within seconds, allowing experimentation with different planning objectives.

3.1 Regional Model of the Prostate

Calculating the TCP requires that the tumor cell density is known for every part of the prostate. This information can be derived from multi-parametric MRI, however, for the purpose of this study, the prostate is divided into several regions, with a single tumor cell density for each region [7]. Ultrasound scans taken at 5mm intervals give a sequence of 2-dimensional slices of the prostate, showing the contour of the organ itself and the urethra. The prostate is divided into upper, central and lower slices, each of which is further divided into 16 rectangles, yielding 48 regions. Each region is assigned one of five tumor cell density categories according to tumor location statistics determined in a study by Zeng et al. [19].

3.2 Placement Constraints

The following constraints apply to all patients. The seeds must be placed on the points of a 5mm x 5mm x 5mm grid. This restriction is due to the method of delivery, where needles are inserted through a metal template with holes at a 5mm x 5mm spacing. Ultrasound scans are also taken at a 5mm spacing. No two seeds may be adjacent – at neighbouring grid points – in any axis-aligned direction. That is, the presence of a seed at a grid point excludes a seed in any of its six orthogonal neighbours. The intention is to prevent a local region from having a severely high dose.

No needle may be placed in the central column of grid points. The grid is aligned such that the central column coincides with the urethra; any needle placed in this column risks perforating the urethra. Seeds must be placed inside the planning target volume (PTV), or within 5mm posteriorly or laterally of the PTV. However, seeds may not be placed between the PTV and the rectum. A needle must not deliver only one seed – if a needle is used, it must deliver at least two seeds. This restriction is so that the tissue is not perforated any more than necessary.

The following dose-related constraints are user-customizable for each patient. The dose received by the urethra must be restricted. For example, the volume of the urethra which receives a dose of more than 217 Gray (which is 150% of the conventional, whole gland prescribed dose of 145 Gray) is limited to at most 10%. There may be more than one such constraint on the urethral dose, each at different thresholds. Similar constraints may be placed on the dose received by the rectum.

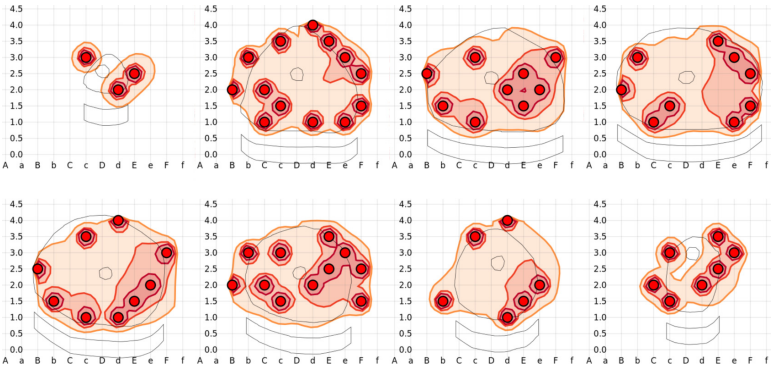

Figure 2: Sample seed plan created by the optimization algorithm

3.3 Focal Plan Optimization Algorithm

The goal of the optimization algorithm is to determine where to place the seeds so that the TCP is as high as possible while maintaining the dose threshold constraints on critical structures such as the urethra and rectum. In addition to the dose constraints, there are anatomical restrictions that restrict certain arrangements of seeds. Figure 2 shows a seed plan created by the algorithm, illustrating seed positions, dose contours and physical structures.

Algorithm 1 improves a plan using local search. It begins with an empty configuration, having no seeds, and at each step it takes the best configuration found so far. It calls IMPROVE to try to find a small change that leads to a better configuration. The IMPROVE procedure is called repeatedly until a sufficiently good plan is found or the user terminates the search.

Algorithm 1 Improve on the current best seed plan.

```
1:  procedure IMPROVE(best)
2:      configuration ← best ;  prob ← U(0.1, 0.9)
3:      for needle N in configuration do
4:          delete needle N from configuration with probability prob
5:      loop:
6:      moves ← random selection of 150 moves
7:      for m ∈ moves do
8:          c ← configuration resulting from executing m on configuration
9:          compute doses for c
10:         if c violates constraints then
11:             discard c and continue with next move
12:         compute TCP of c
13:         if TCP of c is better than TCP of configuration then
14:             configuration ← c
15:             goto loop
16:     if TCP of configuration is better than TCP of best then
17:         return configuration
18:     else return best
```

A *needle* **N** is a set of seeds on the 5mm x 5mm x 5mm grid that have the same x and y coordinates. The set of moves considered on line 6 is the union of possible needle *additions*, *rearrangements* and *replacements*. The possible needle additions are every combination of

needle position (i.e. x-y pair) inside the target volume and seed positions on that x-y line, such that none of the seeds lie on adjacent grid positions. The possible needle rearrangements are every possible rearrangement of the seeds inside a single needle in the configuration. That is, for a chosen needle, the seeds inside that needle are discarded and a new set is inserted as for a needle addition above. The possible needle replacements are every possible combination of a deletion of an existing needle and an addition (as above) of a new needle.

3.4 Search Efficiency

To make the search as efficient as possible, we limit the amount of recalculation required when considering moves. The moves are chosen so that they preserve as many of the constraints as possible, to reduce the number of moves that must be trivially discarded. The seeds-per-needle constraint is always preserved, and when adding seeds, only legal seed positions are considered. It is straightforward to add any other constraints, e.g. limiting the total number of seeds or needles, or the dose in a certain region.

The dose calculation is the most computationally expensive part of the search algorithm. The dose at each sample point is computed as the sum of the doses contributed by each seed in the plan, giving a complexity for a naive algorithm of $O(nm)$, with the number of seeds n typically between 50 and 100 and the number of sample points m typically in the thousands.

We take advantage of the additive nature of the dose calculation. When a seed is added to the plan, only the new seed's contribution is added, keeping the contributions from the existing seeds. (Similarly, for a removed seed we subtract its contribution.) This incremental approach reduces the complexity to $O(m)$.

In addition, some care is taken to make the dose calculation itself as efficient as possible. The major expense of the calculation is the evaluation of a piecewise-linear function defined by a lookup table. We experimented with several methods of calculating this function, ultimately unrolling the entire lookup loop into a series of simple branches.

Using these techniques, the optimization algorithm can find sufficiently good plans within a few seconds in all cases we have tried, including those in Section 5.

4 Post-operative seed displacement

Discrepancies commonly occur between the planned seed placement and the actual, post-operative, seed location. This is due to a number of factors including deformation of the prostate as needles are inserted, swelling, inaccuracy in needle placement, and post-implant seed migration [3]. This discrepancy has the potential to significantly affect the radiation dose distribution to the prostate and surrounding organs and structures [16, 2]. Because the focal plans proposed in this research are designed to deliver location-specific radiation doses as well as a lower dosage to the prostate overall, seed displacement has the potential to undermine the efficacy of this form of treatment. To address this, the amount of seed displacement observed in clinical patients is modelled from (pre-operative) treatment plan and the post-operative computed tomography (CT) images. The efficacy of the clinical plans created manually and the focal plans obtained using computational optimisation are then evaluated subject to the modelled seed displacement.

4.1 Comparing Pre- and Post-operative Seed Plans

To evaluate the post-operative displacement in the x, y and z axes, the seeds in the pre-treatment plan are matched to those in the post-operative CT images by creating pairs of seeds which minimise the total squared displacement across the entire prostate. Algorithm 2 uses simulated annealing to match the pairs. Pre-treatment of the data is limited to the creation

of dummy seeds to obtain an equal number of pre and post operative seeds. The cause of this anomaly is due to (a) seed migration out of the prostate via blood vessels or (b) the insertion of extra unplanned seeds during the implant surgery when a radiation oncologist determines that additional dosing is required to a certain region in theatre.

Algorithm 2 Find pairing between pre- and post-operative seed positions.

Inputs *Ipre* and *Ipost* are vectors of tuples (x_i, y_i, z_i, k_i) where x_i, y_i, z_i are the seed location and k_i is an indicator variable where $k_i = 1$ if the seed is real and $k_i = 0$ if the seed is a dummy.

procedure FINDPAIRING(*Ipre*, *Ipost*)

$maxseeds \leftarrow \max(M, N)$

if $N > M$ **then** append $(maxseeds - M)$ dummy (0,0,0,0) seeds to *Ipre*

if $N < M$ **then** append $(maxseeds - N)$ dummy (0,0,0,0) seeds to *Ipost*

$Ipre_i \leftarrow (x_i - \overline{x},\ y_i - \overline{y},\ z_i - \overline{z},\ k_i)$; $Ipost_j \leftarrow (x_j - \overline{x},\ y_j - \overline{y},\ z_j - \overline{z},\ k_j)$

$count \leftarrow 0$

repeat

$S_{max} \leftarrow \sum_{i=1}^{maxseeds} (k_{Pre_i})(k_{Post_i})||Ipre_i - Ipost_i||^2$

choose a_1, a_2 uniformly from $(0, maxseeds)$

swap $Ipost_{a_1}$ and $Ipost_{a_2}$; calculate S_{swap} as for S_{max}

if $S_{swap} < S_{max}$ or $random\ U[0, 1] > 1 - \exp(\frac{-count}{\Lambda})$ **then**

$S_{max} \leftarrow S_{swap}$

else undo swap

$count \leftarrow count + 1$

until S_{max} unchanged for T iterations

4.2 Analysis of Post-operative Displacement of Clinical Plans

The clinical plans of the patients selected for this study were analysed to determine the distribution of post-operative seed displacement that had occurred in actual treatments. 10 patients were selected for this study; their selection is described in Section 5. Seed displacement for all patients in each of the x, y and z directions is approximately normally distributed, having mean 0mm and standard deviation approximately 3.8mm. Distributional form was confirmed by visual inspection and by a normal probability plot for each data set. These results were consistent with those obtained by Bues et al. [3], using visual inspection on a small data set. In the robustness analysis of the focal plans following, the treatment plans are subject to normally distributed displacements and the effect on TCP and dose to organs at risk is analysed.

5 Evaluation of Focal Plans

Three focal plans were designed for clinical patients who had previously received conventional low dose-rate brachytherapy over the whole prostate. Ten consecutive patients were selected from the Peter MacCallum Cancer Centre for this retrospective Human Research Ethics Committee-approved study. The focal plans are: FocalA, where the objective is to achieve TCP of 0.90 - 0.95, with the volume of urethra receiving 125% of conventional dose less than 10%; FocalB is based on FocalA but allowing the planner to edit the machine-optimised plan; FocalC is computed with a TCP objective of 0.80 - 0.85. The performance of these focal plans and the original clinical plan is evaluated under different levels of post-operative displacement. For

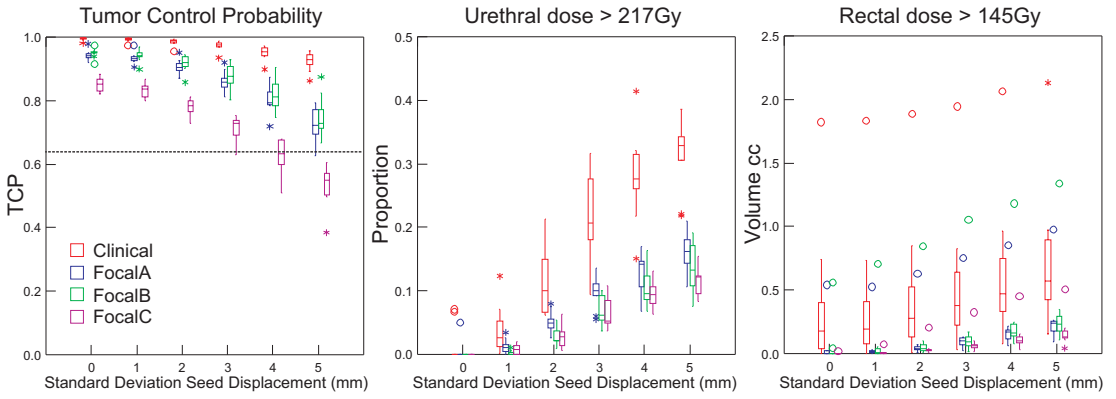

Figure 3: TCP, urethral and rectal doses as function of seed displacement

comparison, the original clinical plan is also evaluated under the same conditions.

The TCP indicates the effectiveness of the brachytherapy treatment. The proportion of the urethra receiving a dose equal to or greater than 217 Gray (150% of the conventional, whole gland prescribed dose), and the volume of the rectum receiving a dose equal to or greater than 145 Gray (100% of the conventional dose), indicate the risk of adverse side effects [4]. The focal plans were created using each patient's 3 dimensional map of the prostate in x = 2mm, y = 2mm, z = 5mm voxels, with each voxel assigned an initial clonogen number indicating the probability of finding tumor cells in that voxel. Other parameters in the TCP calculations are from [7].

The generated focal plans in all cases require significantly fewer seeds and needles than the clinical plans. The clinical plans required, on average, 85 seeds and 28 needles whereas Focal plans A and B required 73 seeds and 23 needles, resulting in lower overall radiation dosage to the prostate as well as less trauma caused by the brachytherapy operation. The focal plans all achieved the desired TCP values.

5.1 Robustness of clinical and focal plans to post-operative seed displacement

To test the robustness of the treatment plans, we simulated displacements that typically occur post-operatively. Each plan was subject to varying levels of seed displacement and the effect on performance measures recorded. Displacements were simulated as normally distributed random variables in each of the x, y and z directions, having mean 0 and standard deviations of 1, 2, 3, 4, 5mm. Every seed was displaced in each trial. 100 trials were run at each level and the average value of each performance measure calculated.

The TCP for each plan as a function of seed displacement is shown in Figure 3. It can be seen that TCP values for all plans degrade as seed displacement increases. The clinical plan and Focal plans A and B are robust to small amounts of displacement with a very small effect on TCP observed for small displacements. Even at the largest displacement tested, these plans all maintain TCP values in excess of 0.62 (as indicated in the figure), which is the minimum TCP required with the current set of input parameters for a high degree of biochemical control [7]. Focal plan C degrades more rapidly than the other plans, and at higher levels of displacement results in TCP values below the minimum required for biochemical control. Thus it is likely that these plans would not be acceptable in clinical settings without measures in place to ensure post-implant accuracy.

Figure 3 also illustrates how focal plans could reduce potential side effects of brachytherapy. It is evident for all plans that as post-operative seed displacement increases the amount of radiation to the urethra and the rectum also increases. The focal plans, by design, produce very small levels of radiation in the urethra and rectum, and preserve this even as seed displacement increases. In the case of the urethra, the proportion receiving 150% of the conventional, whole gland prescribed dose is about half that given by the clinical plan, with this proportion remaining constant as seed displacement increases. For rectal doses, the advantage of focal plans is even greater, with doses approximately one third of that given by the clinical plan across all levels of seed displacement.

6 Summary and Conclusion

This paper has presented an algorithm for optimizing the seed placement for focal brachytherapy treatment. It enables plans to be created more quickly than current manual methods, to focus the radiation dose on known tumor locations while keeping a lower radiation dose on other regions of the prostate.

We have also demonstrated that the focal plans generated by the algorithm are robust to post-operative movement of the seeds, within the range of variability that is observed in clinical practice. Overall, the focal plans offer high treatment efficacy and reduced radiation dose in the tissue in the urethra and rectum.

The next stage of research is to better integrate the optimization with the robustness modelling in order to obtain patient treatment plans that minimize radiation dose to surrounding organs even in the presence of post-operative seed displacement.

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References

[1] AIHW 2013. *Prostate cancer in Australia*. Canberra: Australian Institute of Health and Welfare, 2013.

[2] Luc Beaulieu, Louis Archambault, Sylviane Aubin, E Oral, Richard Taschereau, and Jean Pouliot. The robustness of dose distributions to displacement and migration of ^{125}I permanent seed implants over a wide range of seed number, activity, and designs. *International Journal of Radiation Oncology · Biology · Physics*, 58(4):1298–1308, 2004.

[3] Martin Bues, Edward J Holupka, Paul Meskell, and Irving D Kaplan. Effect of random seed placement error in permanent transperineal prostate seed implant. *Radiotherapy and oncology*, 79(1):70–74, 2006.

[4] Brian J. Davis, Eric M. Horwitz, W. Robert Lee et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy*, 11(1):6–19, 2012.

[5] Peter Grimm, Ignace Billiet, David Bostwick et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk

prostate cancer treatment by radical therapy. results from the prostate cancer results study group. *BJU International*, 109:22–29, 2012.

[6] Annette Haworth, Martin Ebert, David Waterhouse, David Joseph, and Gillian Duchesne. Assessment of I-125 prostate implants by tumor bioeffect. *International Journal of Radiation Oncology · Biology · Physics*, 59(5):1405–1413, 2004.

[7] Annette Haworth, Scott Williams, Hayley Reynolds, David Waterhouse, Gillian M. Duchesne, Joseph Bucci, David Joseph, Sean Bydder, and Martin Ebert. Validation of a radiobiological model for low-dose-rate prostate boost focal therapy treatment planning. *Brachytherapy*, 12(6):628–636, 2013.

[8] IARC. Globocan 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. `http://globocan.iarc.fr`. Retrieved 2014-12-16.

[9] Mira Keyes, Stacy Miller, Veronika Moravan, et al. Predictive factors for acute and late urinary toxicity after permanent prostate brachytherapy: Long-term outcome in 712 consecutive patients. *International Journal of Radiation Oncology · Biology · Physics*, 73(4): 1023–1032, 2008.

[10] Stephen Langley, Hashim U. Ahmed, Bashar Al-Qaisieh, et al. Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer. *BJU International*, 109 (s1):7–16, 2012.

[11] Eva K Lee, Richard J Gallagher, David Silvern, Cheng-Shie Wuu and Marco Zaider. Treatment planning for brachytherapy: an integer programming model, two computational approaches and experiments with permanent prostate implant planning. *Physics in Medicine and Biology*, 44(1):145–165, 1999.

[12] Subir Nag, Jay P. Ciezki, Robert Cormack et al. Intraoperative planning and evaluation of permanent prostate brachytherapy: report of the American Brachytherapy Society. *International Journal of Radiation Oncology · Biology · Physics*, 51(5):1422–1430, 2001.

[13] Mark J Rivard, Bert M Coursey, Larry A DeWerd, et al. Update of AAPM Task Group no. 43 report: A revised AAPM protocol for brachytherapy dose calculations. *Medical physics*, 31(3):633–674, 2004.

[14] Kurt M Snyder, Richard G Stock, Suzanne M Hong, Yeh Chi Lo, and Nelson N Stone. Defining the risk of developing grade 2 proctitis following ^{125}I prostate brachytherapy using a rectal dose–volume histogram analysis. *International Journal of Radiation Oncology · Biology · Physics*, 50(2):335–341, 2001.

[15] Nelson N Stone and Richard G Stock. Long-term urinary, sexual, and rectal morbidity in patients treated with iodine-125 prostate brachytherapy followed up for a minimum of 5 years. *Urology*, 69(2):338–342, 2007.

[16] Richard Taschereau, Jean Roy, and Jean Pouliot. Monte Carlo simulations of prostate implants to improve dosimetry and compare planning methods. *Medical physics*, 26(9): 1952–1959, 1999.

[17] Massimo Valerio, Hashim U. Ahmed, Mark Emberton, et al. The role of focal therapy in the management of localised prostate cancer: A systematic review. *European Urology*, 66 (4):732–751, 2014.

[18] Scott G. Williams, Jeremy L. Millar, Gillian M. Duchesne, Michael J. Dally, Peter L. Royce, and Ross M. Snow. Factors predicting for urinary morbidity following ^{125}iodine transperineal prostate brachytherapy. *Radiotherapy and Oncology*, 73(1):33–38, 2004.

[19] Jianchao Zeng, John J Bauer and Seong K Mun. Modeling and mapping of prostate cancer. *Computers & Graphics*, 24(5):683–694, 2000.